Chapter-2

Synthesis of Imines
Introduction:
Imines are generally known as Schiff bases to honour Prof. Hugo Schiff, since their synthesis was first reported by Schiff [1]. Structurally, imine is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C\(\text{O}\)) has been replaced by an imine or azomethine group. The condensation of primary amines with aldehydes and ketones give imines. Imines that contain an aryl group bound to the nitrogen or to the carbon atom are called Schiff bases.

\[
\begin{align*}
R^1 & \quad C=\text{N} \quad R^3 \\
R^2 & \\
\end{align*}
\]

\(R^1, R^2, R^3\) = aryl or alkyl

General structure of imine

Imines of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic aldehydes, having an effective conjugation system, are more stable. Imines are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilisers. Imines have number of applications viz., preparative use, identification, detection and determination of aldehydes or ketones, purification of carbonyl or amino compounds, or protection of these groups during complex or sensitive reactions.

The chemistry of the carbon-nitrogen double bond plays a vital role in the progress of chemistry science [2]. The mechanism of transformation of aldehydes and amines in to Imine or Schiff bases, involved in two steps. In step one, there is nucleophilic attack of primary amine on carbonyl carbon affords hydroxyl compound which on dehydration gives imine. The formation of imine in the second step largely depends upon the rate of removal of water from reaction mixture. The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation [3-4]. Molecular sieves are then used to completely remove water formed in the system [5]. In the 1990s an in situ method for water elimination was developed, using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate [6-7]. Synthesis of imine is often carried out with acid-catalyzed and generally by refluxing the mixture of aldehyde (or ketone) and amine in organic medium.
In 2004, Chakraborti et al. [8] demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. They proposed as an alternative the use of substances that function as Bronsted-Lowry or Lewis acids to activate the carbonyl group of aldehydes, catalyze the nucleophilic attack by amines, and dehydrate the system, eliminating water as the final step. Examples of Bronsted-Lowry or lewis acids used for the synthesis of imines include ZnCl$_2$, TiCl$_4$, MgSO$_4$·PPTS, Ti(OR)$_4$, alumina, H$_2$SO$_4$, NaHCO$_3$, MgSO$_4$, Mg(ClO$_4$)$_2$, CH$_3$COOH, P$_2$O$_5$/Al$_2$O$_3$, HCl [9-20]. In the past 12 years a number of innovations and new techniques have been reported, including solvent-free/clay/microwave irradiation, solid-state synthesis, K-10/microwave, water suspension medium, BF$_4$/molecular sieves, infrared irradiation/no solvent, NaHSO$_4$/microwave/solvent-free/CaO/microwave, and silica/ultrasound irradiation [21-29]. Among these innovations, microwave irradiation has been extensively used due to its operational simplicity, enhanced reaction rates, and great selectivity [32]. The use of microwave irradiation commenced with the independent studies of Rousell and Majetich groups [30-31]. Microwave irradiation is less environmentally problematic than other methods because it abolishes the excessive use of aromatic solvents and the Dean-Stark apparatus for azeotropic removal of water. Synthesis of imines have been described in variant conditions using sulphuric acid and glacial acetic acid to get efficient yield. Chemistry of imine has been intensively investigated in recent years, owing to their coordination properties and diverse biological applications.

**Biological activity spectrum of Imines:**

Imines derivatives are very important because of their varied structures and biological activities [32-33]. They are the important compound owing to their wide range of biological activities and industrial application. they have been found to posses the pharmacological activities such as antimicrobial [34-39], antipathogenic [40-41], antidepressant [42], antiviral [43-44], antitcancer [45-46], Fungicide [47-48], bactericide [49-50], Cytotoxicity [51], herbicide [52], insecticide [53-54], antioxidant agent [55-56], antiproliferative [57-58].

The development of bacterial resistance to existing drugs is a major problem in antibacterial therapy and necessitates continuing research into new classes of antibacterials. The increase in the mortality rate associated with infectious diseases is directly related to bacteria that exhibit multiple resistances to antibiotics. The lack of effective treatments is the main cause of this
problem [59-60]. The development of new antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need [61-67]. Arylimino derivatives obtained by the condensation of aromatic amines with isatin are powerful anticonvulsant, antiviral, antibacterial and antifungal agents [68-70].

New Imines of the type, 2-[4-methyl-2-oxo-2H-chromen-7-yl)oxy]-N1-(substituted methylene)acetohydrazides (I) were synthesized by the condensation of aryl/hetero aromatic aldehydes with 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazides under conventional and microwave conditions and characterized through IR, $^1$H NMR and mass spectral data. The synthesized compounds have been screened for antimicrobial activity [71].

![Chemical Structure](image)

Yousif et.al [72] explained the Synthesis of tetra imines of 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene (II) by condensation of 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene with different aromatic aldehydes. The chemical structures were confirmed by means of IR, $^1$H NMR, $^{13}$C NMR, and elemental analysis. All compounds were screened for antibacterial (Staphylococcus aureus ATCC-9144, Staphylococcus epidermidis ATCC-155, Micrococcus luteus ATCC-4698, Bacillus cereus ATCC-11778, Escherichia coli ATCC- 25922, and Pseudomonas aeruginosa ATCC-2853) and antifungal (Aspergillus niger ATCC-9029 and Aspergillus fumigatus ATCC-46645) activities by paper disc diffusion technique.
Bhosale et al. [73] synthesized novel formazan (III) derivatives from condensation of aniline diazonium salt with a variety of imines of 3,4-dimethyl-1H-pyrrole-2-carboxyhydrazide moiety and evaluate their potential antimicrobial and antioxidant activities.

Asiri et al. [74] have synthesized a series of 1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (IV) containing imines characterized and screened for their antibacterial activities. The antibacterial activities (with MIC values) of compounds were evaluated. Compounds showed moderate to good anti-bacterial activity with four bacterial strains, viz. *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium* and *Streptococcus pyogenes*. 

![Chemical structure of formazan (III)](image-url)
The search and development of more effective antifungal agents are mandatory [75-76] and imines are known to be promising antifungal agents. Naqvi et al, [77] have synthesized Imines (V) from 3-chloro-4-fluoro aniline and several benzaldehydes by non classical methods (water based reaction, microwave and grindstone chemistry).

\[
\begin{align*}
\text{(IV)}
\end{align*}
\]

Wadher et al., [78] have been synthesized a series of Imines (VI) 4,4’-diaminodiphenylsulphone was condensed with various aromatic or heterocyclic aldehyde in ethanol in the presence of concentrated sulphuric acid as a catalyst to yield the imine. All these compounds were evaluated for their in vitro activity against several microbes. Compound exhibited potent antibacterial activity with the reference standard ciprofloxacin and fluconazol.

\[
\begin{align*}
\text{(V)}
\end{align*}
\]

\[
\begin{align*}
\text{(VI)}
\end{align*}
\]
Parikh et al., [79] have synthesized and Spectral Studies of some novel imines N-[(1 Z)-1-(4-aminophenyl) ethylidene]-4,6- dimethoxypyrimidin-2-amine (VII) derived with Pyrimidines.

![Image of structure VII]

Singh et al. [80] synthesized a new series of imines bearing N-(4H-1,2,4-triazole-4-yl)benzamido moiety (VIII). Compounds have shown good antibacterial and antifungal activity against Bacillus aureus (Ba), Klebsiella pneumonia (Kp), Pseudomonas aeruginosa (Pa), Gibberella fujikuroi (Gf), Neurospora crassa (Nc) as comparable to standard.

![Image of structure VIII]

Imines are widely studied and used in the fields of organic synthesis and metal ion complexation [81-82] for a number of reasons: their physiological and pharmacological activities [83-85] their use in ion-selective electrodes [86-91] in the determination of heavy metals ions in environmental samples [92] and in the extraction of metals ions [93-94] and their many catalytic applications (e.g. for epoxidation of olefins, alkene cyclopropanation [95-96] trimethylsilylcyanation of ketones [97] asymmetric oxidation of methyl phenyl sulfide enantioselective epoxidation of silylenol [98] and ring-opening polymerization of lactide [99].
It is evident from literature that in imine derivatives the C=N linkage is an essential structural requirement for biological activity. Many attempts have been made to synthesize characterize and to study biological activity of imine. In view of the conclusions drawn from the previous work and looking to the antimicrobial efficacy of sulphonamides like sulphanilimide, sulphamethoxazole, sulphathiazole & sulphadimidine moieties attached to aryl ring it seems logical to combine all these moieties together in a parent molecule. The presence of imine and sulfonamide functional group is responsible for antimicrobial activity, which can be altered depending upon the type of substituent present on the aromatic rings.

Keeping these facts in thoughts several substituted Imines have been synthesized by the condensation of different sulphonamide derivatives with substituted aromatic aldehydes containing allyl and allyloxy group. The study in the present work aimed at exploring the potential antimicrobial compounds containing an imine group (-CH=N).
Experimental Section:

Materials & Methods:
All chemicals and solvents, reagents used in the present study were of analytical grade and solvents were used after distillation. All the melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using precoated TLC plates (MERCK) using n-hexane: ethyl acetate (8:2) solvent system. The developed chromatographic plates were visualized under UV at 254nm. IR spectra were recorded using KBr on Perkin Elmer spectrophotometer. $^1$HNMR spectra in DMSO on a BRUKER FT-NMR instrument using TMS as internal standard and chemical shift values were expressed in ppm. Elemental analysis (CHN) was performed on Carlo Erba 1108.

General procedure for the synthesis of Imines:
A solution of substituted aromatic aldehydes(0.01M in 5mL ethanol) was taken in a flask and sulphonamide derivatives (0.01M : 5mL ethanol) was slowly added with continuous stirring. The contents of the flask were refluxed for four hours and left over night in ice bath. The Imine separated out, collected and further purified by recrystallization from ethanol.
Where $R'=$ 
- [1] p-OH (p position with respect to aldehyde)
- [2] p-CH$_2$=CH-OCH$_2$, o-NO$_2$ (p and o position with respect to aldehyde)
- [3] p-OH, m=CH$_2$=CH-CH$_2$ (p and m position with respect to aldehyde)

$R''=$
- [a] H
- [b] S
- [c] N
- [d] CH$_3$

Scheme of the Reaction
1(a-d) Reaction between 4-hydroxy-3-methoxy benzaldehyde with sulphonamide derivatives:

A solution of substituted 4-hydroxy-3-methoxy benzaldehyde (0.01M: in 5mL ethanol) was taken in a flask and sulphonamide derivatives (0.01M: : 5mL ethanol) was slowly added with continuous stirring. The contents of the flask were refluxed for four hours and left over night in ice bath. The imines separated out, collected and further purified by recrystallization from ethanol.

2(a-d) Reaction between 5-methoxy-2-nitro-(prop-2-en-1-yloxy)benzaldehyde with sulphonamide derivatives:

A solution of substituted 5-methoxy-2-nitro-(prop-2-en-1-yloxy) benzaldehyde (0.01M: in 5mL ethanol) was taken in a flask and sulphonamide derivatives (0.01M: : 5mL ethanol) was slowly added with continuous stirring. The contents of the flask were refluxed for four hours and left over night in ice bath. The imines separated out, collected and further purified by recrystallization from ethanol.

3(a-d) Reaction between 4-hydroxy-3-methoxy-5-(prop-2-en-1-yl)benzaldehyde with sulphonamide derivatives:

A solution of 4-hydroxy-3-methoxy-5-(prop-2-en-1-yl) benzaldehyde (0.01M: in 5mL ethanol) was taken in a flask and sulphonamide derivatives (0.01M: : 5mL ethanol) was slowly added with continuous stirring. The contents of the flask were refluxed for four hours and left over night in ice bath. The imines separated out, collected and further purified by recrystallization from ethanol.
Mechanism of the Reaction
Results:

Physical characteristics of the synthesized imines:

<table>
<thead>
<tr>
<th>S.No</th>
<th>R’</th>
<th>R”</th>
<th>Compound Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P.(°C)</th>
<th>Yield (%)</th>
<th>Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(a)</td>
<td>p-OH</td>
<td>H</td>
<td>C_{14}H_{14}N_{2}O_{4}S</td>
<td>306</td>
<td>200</td>
<td>58</td>
<td>Whitish yellow</td>
</tr>
<tr>
<td>1(b)</td>
<td>p-OH</td>
<td>C_{5}</td>
<td>C_{17}H_{15}N_{3}O_{4}S_{2}</td>
<td>389</td>
<td>150</td>
<td>72</td>
<td>Yellow</td>
</tr>
<tr>
<td>1(c)</td>
<td>p-OH</td>
<td>C_{18}H_{17}O_{5}N_{3}S</td>
<td>387</td>
<td>190</td>
<td>98</td>
<td>Pale yellow</td>
<td></td>
</tr>
<tr>
<td>1(d)</td>
<td>p-OH</td>
<td>C_{20}H_{20}N_{4}O_{4}S</td>
<td>412</td>
<td>110</td>
<td>50</td>
<td>Yellow</td>
<td></td>
</tr>
<tr>
<td>2(a)</td>
<td>p-CH_{2}=CH-OCH_{2}, o-NO_{2}</td>
<td>H</td>
<td>C_{17}H_{17}N_{3}O_{6}S</td>
<td>391</td>
<td>120</td>
<td>66</td>
<td>Yellow</td>
</tr>
<tr>
<td>2(b)</td>
<td>p-CH_{2}=CH-OCH_{2}, o-NO_{2}</td>
<td>C_{5}</td>
<td>C_{20}H_{18}N_{4}O_{6}S_{2}</td>
<td>474</td>
<td>110</td>
<td>70</td>
<td>Brown yellow</td>
</tr>
<tr>
<td>2(c)</td>
<td>p-CH_{2}=CH-OCH_{2}, o-NO_{2}</td>
<td>C_{21}H_{20}N_{4}O_{7}S</td>
<td>472</td>
<td>120</td>
<td>75</td>
<td>Yellow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Molecular Formula</td>
<td>Molecular Mass</td>
<td>Melting Point</td>
<td>Appearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
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<td>----------------</td>
<td>--------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2(d)</td>
<td>p-CH₂=CH-OCH₂, o-NO₂</td>
<td>C₂₃H₂₅N₅O₆S</td>
<td>497</td>
<td>130</td>
<td>60</td>
<td>Brown yellow</td>
<td></td>
</tr>
<tr>
<td>3(a)</td>
<td>p-OH, m=CH₂=CH-CH₂</td>
<td>C₁₇H₁₈N₂O₄S</td>
<td>346</td>
<td>75</td>
<td>72</td>
<td>Yellow</td>
<td></td>
</tr>
<tr>
<td>3(b)</td>
<td>p-OH, m=CH₂=CH-CH₂</td>
<td>C₂₀H₁₉N₃O₄S₂</td>
<td>429</td>
<td>65</td>
<td>80</td>
<td>Cremish yellow</td>
<td></td>
</tr>
<tr>
<td>3(c)</td>
<td>p-OH, m=CH₂=CH-CH₂</td>
<td>C₂₁H₂₁N₃O₅S</td>
<td>427</td>
<td>70</td>
<td>95</td>
<td>Cremish white</td>
<td></td>
</tr>
<tr>
<td>3(d)</td>
<td>p-OH, m=CH₂=CH-CH₂</td>
<td>C₂₃H₂₄N₄O₄S</td>
<td>452</td>
<td>65</td>
<td>82</td>
<td>Brown yellow</td>
<td></td>
</tr>
</tbody>
</table>
I.R. and N.M.R . Spectral data of Imine:

\[
\text{1(a) 4-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]amino} \text{ benzenesulfonamide}
\]

<table>
<thead>
<tr>
<th>Absorption Frequencies (cm(^{-1}))</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>3389.8</td>
<td>O-H</td>
</tr>
<tr>
<td>1670.7</td>
<td>CH=N</td>
</tr>
<tr>
<td>1139.85</td>
<td>S=O</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NMR Spectra(DMSO-d)</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>s,1H,OH</td>
</tr>
<tr>
<td>7.5</td>
<td>s,1H,CH=N</td>
</tr>
<tr>
<td>3.7-7.9</td>
<td>m,12H, Ar-H</td>
</tr>
</tbody>
</table>
4-[(E)-(4-hydroxy-3-methoxyphenyl) methylidene]aminotoluene sulfonyl amide
References:


